STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 102880

TO: Dwayne C Jones **Location: CM1/2D07&2D01** **Art Unit: 1614** **Monday, September 15, 2003** **Case Serial Number: 09/895463**	**From: Barb O'Bryen** **Location: Biotech-Chem Library** **CM1-6A05** **Phone: 308-4291** BOB **barbara.obryen@uspto.gov**

Search Notes

Background

5,559,269 (5-HM)

5,686,464 (5-HM)

4 of 21 ≅

9 of 21 WO 2001/034139
WO 2000/027364

11 of 21

12 of 21 US 6,313,132
or
WO 98/43642

14 of 21 6,517,864

≅ get 5,382,600
treatment of overactive bladder

=> fil reg; d stat que l108; fil capl; d que nos l111; fil toxcenter; d que nos l112; fil biosis; d que nos l113; fil uspatfull uspat2; d que nos l120
FILE 'REGISTRY' ENTERED AT 14:30:15 ON 15 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2003 HIGHEST RN 585509-69-9
DICTIONARY FILE UPDATES: 14 SEP 2003 HIGHEST RN 585509-69-9

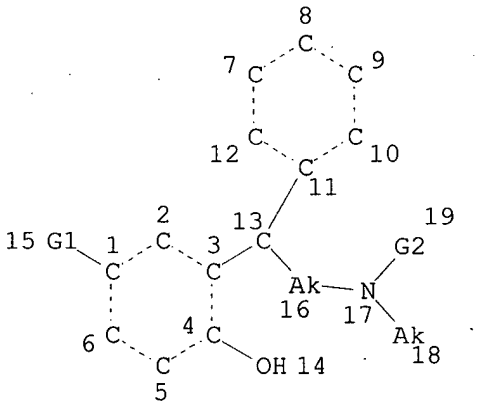
TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L4 STR



full file search done on this structure

VAR G1=22/20
VAR G2=H/22
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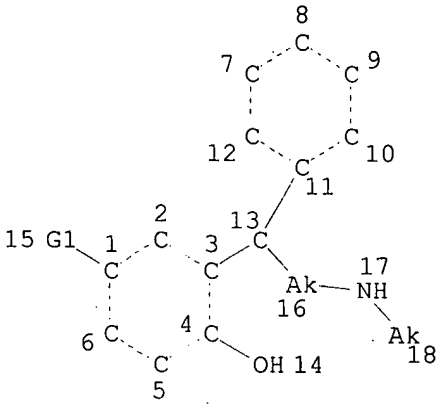
CONNECT IS E1 RC AT 18
CONNECT IS E2 RC AT 20
CONNECT IS E1 RC AT 22
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L6 61 SEA FILE=REGISTRY SSS FUL L4
L105 STR



Ak—OH
@20 21

Ak @22

VAR G1=22/20
NODE ATTRIBUTES:
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DEFAULT MLEVEL IS ATOM
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NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
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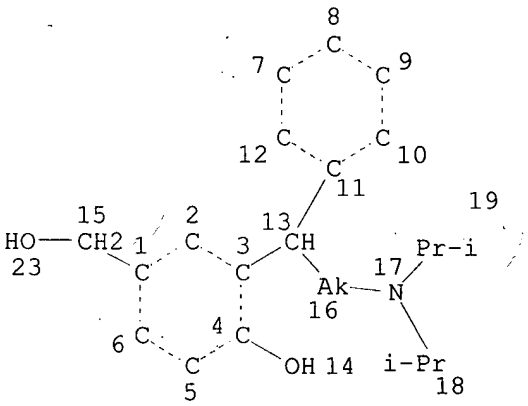

NODE ATTRIBUTES:
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
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GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L108 14 SEA FILE=REGISTRY SUB=L6 SSS FUL (L105 OR L106)

100.0% PROCESSED 61 ITERATIONS 14 ANSWERS
SEARCH TIME: 00.00.01

subset search done looking for either of these 2 structures

```
=> analyze l108
ENTER ANSWER NUMBER OR RANGE (1-):.
ENTER DISPLAY CODE (CHEM) OR ?:lc
L109        ANALYZE L108 1- LC :       7 TERMS

=> d 1-7
L109        ANALYZE L108 1- LC :       7 TERMS

TERM #    # OCC   # DOC   % DOC LC
------ -------- ------ ------ ---------------
     1       14     14 100.00 CA
     2       14     14 100.00 CAPLUS
     3       11     11  78.57 USPATFULL
     4        6      6  42.86 TOXCENTER
     5        2      2  14.29 CASREACT
     6        1      1   7.14 BIOSIS
     7        1      1   7.14 USPAT2
*********  END OF L109 *********
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only these files can have refs with Registry #'s from L108

FILE 'CAPLUS' ENTERED AT 14:30:15 ON 15 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 15 Sep 2003 VOL 139 ISS 12
FILE LAST UPDATED: 14 Sep 2003 (20030914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L4              STR
L6           61 SEA FILE=REGISTRY SSS FUL L4
L16        1803 SEA FILE=CAPLUS ABB=ON  INCONTINEN?/OBI
L17         252 SEA FILE=CAPLUS ABB=ON  URIN?(2A)FREQUEN?/OBI
L18         114 SEA FILE=CAPLUS ABB=ON  POLLAKIUR?
L19         343 SEA FILE=CAPLUS ABB=ON  POLYURI#/OBI
L20       36523 SEA FILE=CAPLUS ABB=ON  SMOOTH(L)MUSCLE#/OBI
L105            STR
L106            STR
L108         14 SEA FILE=REGISTRY SUB=L6 SSS FUL (L105 OR L106)
L110         34 SEA FILE=CAPLUS ABB=ON  L108
L111         12 SEA FILE=CAPLUS ABB=ON  ((L16 OR L17 OR L18 OR L19 OR L20) OR
                POLLAKISURI?) AND L110
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FILE 'TOXCENTER' ENTERED AT 14:30:15 ON 15 SEP 2003

FILE COVERS 1907 TO 9 Sep 2003 (20030909/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/summ2003.html for a description on changes.

```
L4              STR
L6           61 SEA FILE=REGISTRY SSS FUL L4
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L105            STR
L106            STR
L108         14 SEA FILE=REGISTRY SUB=L6 SSS FUL (L105 OR L106)
L112          5 SEA FILE=TOXCENTER ABB=ON  L108


FILE 'BIOSIS' ENTERED AT 14:30:15 ON 15 SEP 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 10 September 2003 (20030910/ED)


L4              STR
L6           61 SEA FILE=REGISTRY SSS FUL L4
L105            STR
L106            STR
L108         14 SEA FILE=REGISTRY SUB=L6 SSS FUL (L105 OR L106)
L113          1 SEA FILE=BIOSIS ABB=ON  L108


FILE 'USPATFULL' ENTERED AT 14:30:15 ON 15 SEP 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 14:30:15 ON 15 SEP 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)


L4              STR
L6           61 SEA FILE=REGISTRY SSS FUL L4
L105            STR
L106            STR
L108         14 SEA FILE=REGISTRY SUB=L6 SSS FUL (L105 OR L106)
L114         11 SEA L108
L115      10080 SEA BLADDER/IT,TI,AB,CLM
L116         57 SEA (POLLAKIURI? OR POLLAKISURI?)/IT,TI,AB,CLM
L117       2064 SEA (SMOOTH(2A) MUSCL?)/IT,TI,AB,CLM
L118        123 SEA (URIN?(3A)(FREQUEN? OR URGEN?))/IT,TI,AB,CLM
L119       3178 SEA INCONTINEN?/IT,TI,AB,CLM
L120          8 SEA L114 AND (L115 OR L116 OR L117 OR L118 OR L119)


=> dup rem l111,l120,l113,l112
FILE 'CAPLUS' ENTERED AT 14:30:26 ON 15 SEP 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATFULL' ENTERED AT 14:30:26 ON 15 SEP 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 14:30:26 ON 15 SEP 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'TOXCENTER' ENTERED AT 14:30:26 ON 15 SEP 2003
COPYRIGHT (C) 2003 ACS
PROCESSING COMPLETED FOR L111
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PROCESSING COMPLETED FOR L120
PROCESSING COMPLETED FOR L113
PROCESSING COMPLETED FOR L112
L121          21 DUP REM L111 L120 L113 L112 (5 DUPLICATES REMOVED)
                 ANSWERS '1-12' FROM FILE CAPLUS
                 ANSWERS '13-19' FROM FILE USPATFULL
                 ANSWER '20' FROM FILE BIOSIS
                 ANSWER '21' FROM FILE TOXCENTER

=> d ibib abs hitstr 1-19; d iall 20-21

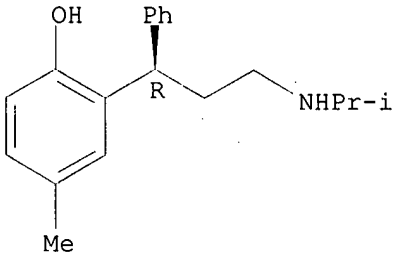
L121 ANSWER 1 OF 21  CAPLUS  COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2003:22634  CAPLUS
DOCUMENT NUMBER:          138:66708
TITLE:                    Tolterodine metabolites for the treatment of
                          smooth muscle hyperactivity
INVENTOR(S):              Aberg, A. K. Gunnar
PATENT ASSIGNEE(S):       Bridge Pharma, Inc., USA
SOURCE:                   PCT Int. Appl., 15 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ---------------   ----  --------      ---------------   --------
     WO 2003002059      A2   20030109      WO 2002-US20257   20020626
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2003027856      A1   20030206      US 2001-895463    20010629
PRIORITY APPLN. INFO.:                    US 2001-895463    A  20010629
AB   Methods are disclosed for treating smooth muscle hyperactivity, including
     urinary incontinence, while avoiding concomitant liability of adverse
     effects assocd. with tolterodine and the racemic version thereof.  The
     methods comprise administering a therapeutically effective amt. of a
     mono-iso-Pr metabolite or a parahydroxymethyl metabolite or a
     parahydroxymethyl mono-iso-Pr metabolite of tolterodine or racemic
     versions thereof or a pharmaceutically acceptable salt of either
     metabolite.  Pharmaceutical compns. in the form of tablets and transdermal
     devices comprising said compds. and acceptable carriers are also
     disclosed.
IT   194482-41-2 194482-42-3 200801-70-3
     207679-81-0 480432-14-2 480432-16-4
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (tolterodine metabolites for treatment of smooth
        muscle hyperactivity)
RN   194482-41-2  CAPLUS
CN   Phenol, 4-methyl-2-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI)
     (CA INDEX NAME)

Absolute stereochemistry.  Rotation (+).
```

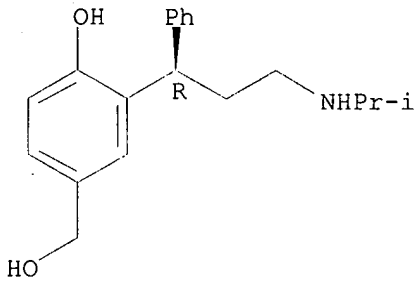
applicant

priority dt



RN 194482-42-3 CAPLUS
CN Benzenemethanol, 4-hydroxy-3-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 200801-70-3 CAPLUS
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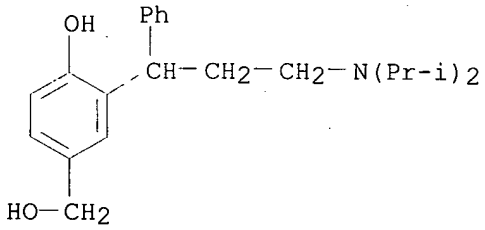
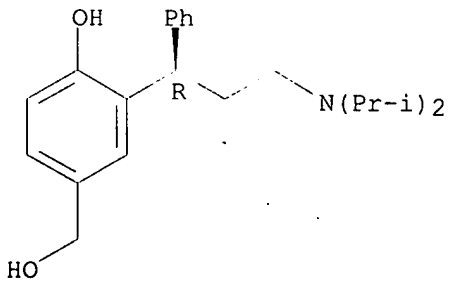
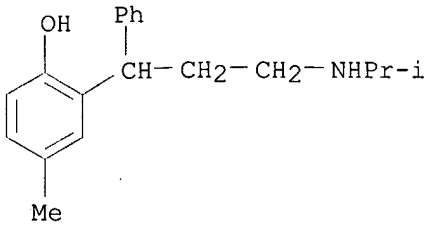


RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

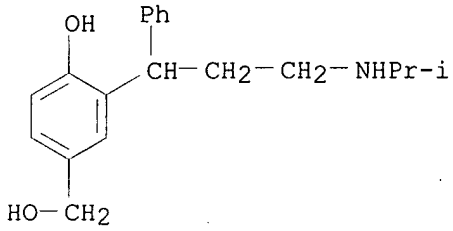
Absolute stereochemistry. Rotation (+).



RN 480432-14-2 CAPLUS
CN Phenol, 4-methyl-2-[3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



RN 480432-16-4 CAPLUS
CN Benzenemethanol, 4-hydroxy-3-[3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



L121 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:242003 CAPLUS
DOCUMENT NUMBER: 138:260465
TITLE: Pharmaceutical composition comprising receptor agonists and antagonists treatment of urinary disorder
INVENTOR(S): Arneric, Stephen P.; Andersson, Per-Olof
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003060513	A1	20030327	US 2001-965556	20010927
WO 2003026564	A2	20030403	WO 2002-SE1748	20020926

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-965556 A 20010927
SE 2001-3858 A 20011120

AB The present invention concerns the field of urol. The invention provides

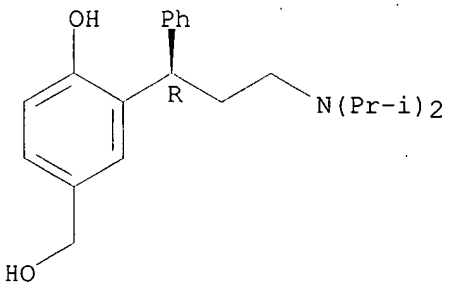
a novel pharmaceutical compn., comprising a pharmaceutically effective combination of (i) a first compd. selected from the group consisting of muscarinic receptor antagonists, 5.alpha.-reductase inhibitors, and .alpha.-adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and (ii) a second compd. selected from the group consisting of 5-HT1a receptor agonists and antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor. There is also provided a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amt. of a compn. according to the invention. A pharmaceutical compn. contained between about 2 mg to about 20 mg of 5a-reductase inhibitor and between about 0.5 mg to about 50 mg of neutral 5-HT1a receptor antagonist. The compn. is administered to a patient for the treatment of urinary disorder.

IT **207679-81-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compn. comprising receptor agonists and antagonists treatment of urinary disorder)

RN 207679-81-0 CAPLUS

CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L121 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2002:17140 CAPLUS

DOCUMENT NUMBER: 136:226330

TITLE: The effect of tolterodine on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive containing ethinyl estradiol and levonorgestrel

AUTHOR(S): Olsson, Birgitta; Landgren, Britt-Marie

CORPORATE SOURCE: Experimental Medicine, Biovitrum AB, Stockholm, Swed.

SOURCE: Clinical Therapeutics (2001), 23(11), 1876-1888
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Excerpta Medica, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

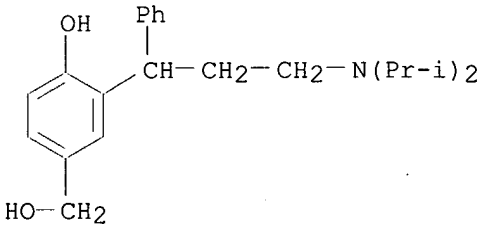
AB Background: Tolterodine is an antimuscarinic agent for the treatment of overactive bladder, a chronic condition that is particularly common in women. Given the prevalence pattern of overactive bladder and the widespread use of oral contraception, circumstances are likely to arise in which physicians may wish to prescribe tolterodine for patients already taking oral contraceptives. Based on a search of MEDLINE from 1990 to 2001, there have been no studies of whether concomitant use of these agents entails a risk of drug-drug interaction or conception. Objective: This study investigated the effects of tolterodine on the pharmacokinetics and pharmacodynamics of a low-dose combination oral contraceptive (ethinyl

estradiol 30 .mu.g/levonorgestrel 150 .mu.g). Methods: This was an open-label, randomized, 2-period crossover study in healthy women. Oral contraception was given for 21 days either alone or in combination with oral tolterodine 2 mg BID (on days 1-14) over two 28-day contraceptive cycles. Pharmacokinetic assessments were performed on day 14 based on plasma levels of ethinyl estradiol and levonorgestrel up to 24 h after dosing and serum tolterodine levels at 1 to 3 h after dosing. The potential for pharmacodynamic interaction was assessed in terms of the risk of failure of suppression of ovulation based on serum levels of estradiol and progesterone measured throughout each cycle. Results: Twenty-four healthy women (age, 23-41 yr [mean, 30 yr]; height, 155-178 cm [mean, 167 cm]; body wt., 51-75 kg [mean, 64 kg]) participated in the study. There was no evidence of a pharmacokinetic interaction between tolterodine and the steroid hormones in the oral contraceptive used, nor did the oral contraceptive show any relevant pharmacokinetic interaction with tolterodine. Serum levels of estradiol and progesterone indicated suppression of ovulation in both treatment periods. Conclusion: In this selected population, coadministration of tolterodine did not affect the contraceptive efficacy of a low-dose combination oral contraceptive contg. ethinyl estradiol and levonorgestrel.

IT 200801-70-3
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(tolterodine effects on pharmacokinetics and pharmacodynamics of combination oral contraceptive in women)

RN 200801-70-3 CAPLUS

CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 1999:692703 CAPLUS

DOCUMENT NUMBER: 132:87770

TITLE: Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity

AUTHOR(S): Brynne, N.; Forslund, C.; Hallen, B.; Gustafsson, L. L.; Bertilsson, L.

CORPORATE SOURCE: Department of Clinical Pharmacology, Pharmacia and Upjohn AB, Stockholm, SE-112 87, Swed.

SOURCE: British Journal of Clinical Pharmacology (1999), 48(4), 564-572
CODEN: BCPHBM; ISSN: 0306-5251

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

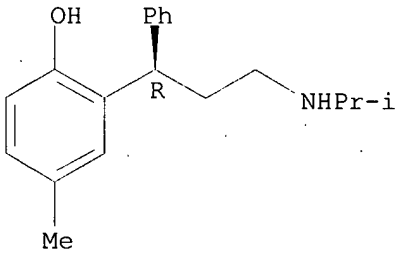
AB The pharmacokinetics and safety of tolterodine and tolterodine metabolites was studied after single-and multiple-dose administration in the absence and presence of ketoconazole, an inhibitor of cytochrome P 450 (CYP) 3A4, in healthy volunteers with deficient CYP2D6 activity, i.e. poor metabolizers of debrisoquine. Eight healthy volunteers received single oral doses (2 mg) of tolterodine L-tartrate. Following a wash-out period

of about 3 mo, six of the subjects participated in a multiple-dose (1 mg twice daily) phase of the study. Ketoconazole 200 mg was given once daily for 4-4.5 days during both the single and multiple dose tolterodine administration phases. Blood samples were drawn and the pharmacokinetics of tolterodine and its metabolites were detd. A decrease ($P < 0.01$) in apparent oral clearance of tolterodine, from 10-12 l h-1 to 4.3-4.7 l h-1, was obtained during concomitant administration of ketoconazole, yielding at least a two-fold increase in the area under the serum concn.-time curve after single as well as after multiple doses following single dose administration of tolterodine. The mean (.+-.s.d.) terminal half-life increased by 50% from 9.7.+-.2.7 h to 15.+-.5.4 h in the presence of ketoconazole. CYP3A4 is the major enzyme involved in the elimination of tolterodine in individuals with deficient CYP2D6 activity (poor metabolizers), since oral clearance of tolterodine decreased by 60% during ketoconazole coadministration. This inhibition resulted in 2.1-fold increase in AUC.

IT **194482-41-2 194482-42-3 207679-81-0,**
PNU-200577
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(as tolterodine metabolite, ketoconazole inhibits the metab. of tolterodine in human subjects with deficient CYP2D6 activity)

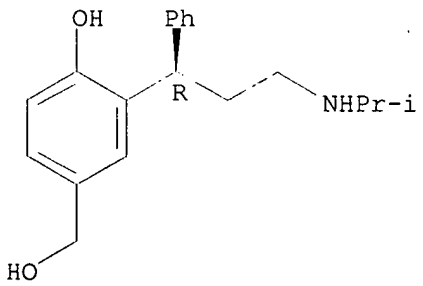
RN 194482-41-2 CAPLUS
CN Phenol, 4-methyl-2-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



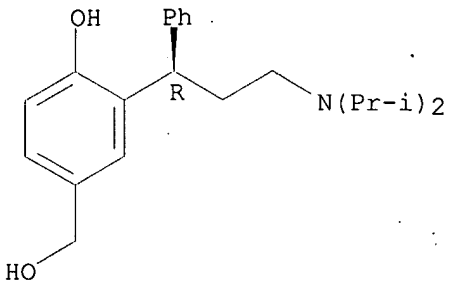
RN 194482-42-3 CAPLUS
CN Benzenemethanol, 4-hydroxy-3-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



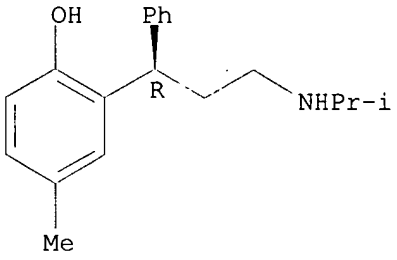
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1999:692702 CAPLUS
DOCUMENT NUMBER: 132:87769
TITLE: Fluoxetine inhibits the metabolism of tolterodine-pharmacokinetic implications and proposed clinical relevance
AUTHOR(S): Brynne, N.; Svanstrom, C.; Aberg-Wistedt, A.; Hallen, B.; Bertilsson, L.
CORPORATE SOURCE: Departments of Clinical Pharmacology, Pharmacia and Upjohn AB, Stockholm, SE-112 87, Swed.
SOURCE: British Journal of Clinical Pharmacology (1999), 48(4), 553-563
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The change in disposition of tolterodine during coadministration of the potent cytochrome P 450 2D6 (CYP2D6) inhibitor fluoxetine was studied. Thirteen patients received tolterodine L-tartrate 2 mg twice daily for 2.5 days, followed by fluoxetine 20 mg once daily for 3 wk and then concomitant administration for an addnl. 2.5 days. They were characterized as extensive metabolizers (EM1 with one functional CYP2D6 gene, EM2 with two functional genes) or poor metabolizers (PM). Nine patients, three EM2 and four EM1 and two PM, completed the trial. Following tolterodine administration, the area under the serum concn.-time curve (AUC) of tolterodine was 4.4-times and 30-times higher among EM1 and PM, resp., compared with EM2. The AUC of the 5-hydroxymethyl metabolite (5-HM) was not quantifiable in PM. Fluoxetine significantly decreased ($P < 0.002$) the oral clearance of tolterodine by 93% in EM2 and by 80% in EM1. The AUC of 5-HM increased in EM2 and decreased in EM1. However, the exposure to the active moiety (unbound tolterodine +5-HM) was not significantly increased in the two phenotypes. The subdivision of the EM group showed a 2.1-fold increase in active moiety in EM2 but the exposure was still similar to EM1 compared with before the interaction. The study suggests a difference in the pharmacokinetics of tolterodine and its 5-hydroxymethyl metabolite depending on the no. of functional CYP2D6 genes. Fluoxetine significantly inhibited the hydroxylation of tolterodine. Despite the effect on the pharmacokinetics of tolterodine in extensive metabolizers, the clin. effect is expected to be within normal variation.

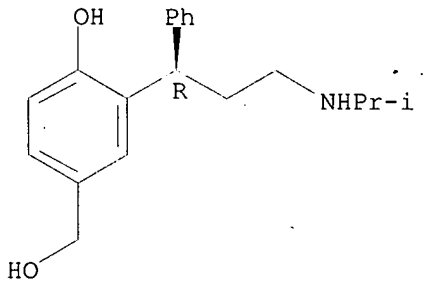
IT **194482-41-2 194482-42-3 207679-81-0,** PNU-200577
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fluoxetine inhibits the metab. of tolterodine-pharmacokinetics)
RN 194482-41-2 CAPLUS
CN Phenol, 4-methyl-2-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



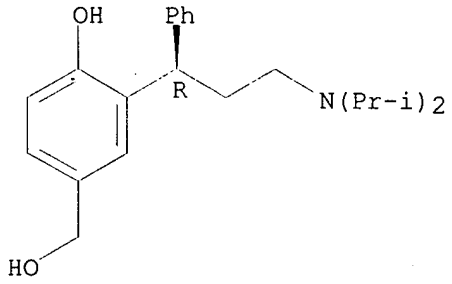
RN 194482-42-3 CAPLUS
CN Benzenemethanol, 4-hydroxy-3-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:376645 CAPLUS
DOCUMENT NUMBER: 138:374201
TITLE: Compositions for treatment of postmenopausal female sexual dysfunction
INVENTOR(S): Bilkey, Chris R.; Slatter, Greg J.; Versi, Ebrahim
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

Searched by Barb O'Bryen, STIC 308-4291

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039553	A1	20030515	WO 2002-US36167	20021112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003118633	A1	20030626	US 2002-289903	20021107
US 2003130244	A1	20030710	US 2002-292742	20021112

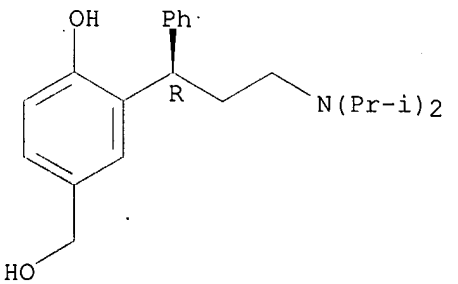
PRIORITY APPLN. INFO.: US 2001-344507P P 20011109

AB A set of pharmaceutical dosage forms is provided, each comprising at least two therapeutic agents selected from (a) an estrogen, (b) an androgen, and (c) an antimuscarinic, in total and relative dosage amts. that are therapeutically effective in treatment of female sexual dysfunction (FSD) or postmenopausal sexual avoidance (PMSA), the dosage forms being adapted for intravaginal administration. A method of treatment of FSD or PMSA comprises administering intravaginally, in a treatment regimen extending over a period of at least 7 days, dosage forms at least a portion of which comprise two or more therapeutic agents selected from (a) an estrogen, (b) an androgen, and (c) an antimuscarinic, in total and relative dosage amts. that are therapeutically effective in treatment of FSD or PMSA, wherein no more than one dosage form is administered on any day. Also provided is a kit useful in implementing such a treatment regimen. For example, a vaginal tablet was formulated contg. 25 g estradiol, 1 mg methyltestosterone, and 2 mg tolterodine tartrate, useful as part of a treatment regimen for PMSA. The estradiol was delivered primarily locally for relief of vaginal dryness, soreness and/or irritation. The methyltestosterone was delivered systematically to increase libido. The tolterodine tartrate was delivered systematically to control urinary incontinence and thereby remove a source of anxiety contributing to PMSA.

IT **207679-81-0**, 5-Hydroxymethyltolterodine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vaginal compns. contg. androgen, estrogen, and antimuscarinic for treatment of postmenopausal sexual dysfunction)

RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:376565 CAPLUS
DOCUMENT NUMBER: 138:390911
TITLE: Antimuscarinic inhalants for treatment of urinary disorder
INVENTOR(S): Cammarata, Sue K.; Kolbasa, Karen; Palandra, Joe; Richards, Ivan; Warchol, Mark P.
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039464	A2	20030515	WO 2002-US35335	20021104
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003144352	A1	20030731	US 2002-287061	20021104

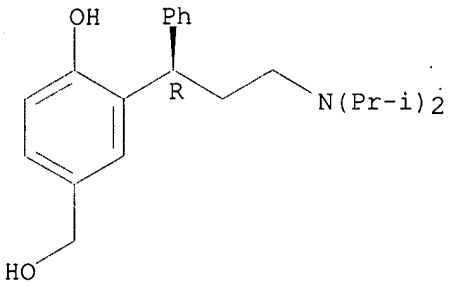
PRIORITY APPLN. INFO.: US 2001-337298P P 20011105

AB The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a. treatment, a therapeutically effective amt. of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation. Furthermore, the present invention provides a pharmaceutical compn. for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable prepn. and comprises a therapeutically effective amt. of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor. The invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manuf. of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders. Tolterodine L-tartrate for aerosol administration was prepd., and administered to patients with overactive bladder to examine the pharmacokinetics.

IT **207679-81-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimuscarinic inhalants for treatment of urinary disorder)

RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

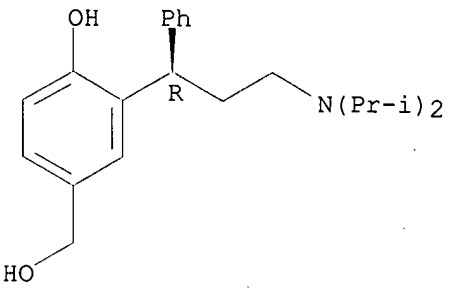


L121 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:63135 CAPLUS
DOCUMENT NUMBER: 139:17122
TITLE: Effect of tolterodine on the anticoagulant actions and pharmacokinetics of single-dose warfarin in healthy volunteers
AUTHOR(S): Rahimy, Mohamad; Hallen, Bengt; Narang, Prem
CORPORATE SOURCE: Dept. of Clinical Pharmacology, Pharmacia Corporation, Kalamazoo, MI, USA
SOURCE: Arzneimittel-Forschung (2002), 52(12), 890-898
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Editio Cantor Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English/German

AB This randomized, double-blind, crossover study investigated the potential effects of tolterodine ((R)-N,N-diisopropyl-3-(2-hydroxy-5-methyl-phenyl)-3-phenylpropanamine, CAS 124937-51-5), an antimuscarinic agent for the treatment of the overactive bladder, on the anticoagulant actions and pharmacokinetics of single-dose warfarin (CAS 81-81-2) in 20 healthy male volunteers. In terms of study design, volunteers randomly received oral tolterodine L-tartrate (2 mg twice daily) or matching placebo for 7 days, with a single oral dose of warfarin (25 mg) administered on day 4 of each treatment period. R-(+)- and S-(-)-warfarin pharmacokinetics were estd. from plasma levels measured up to 96 h post-dose, in conjunction with assessment of prothrombin time and factor VII activity. Pharmacokinetics of tolterodine and its active 5-hydroxymethyl metabolite ((R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethyl-phenyl)-3-phenylpropanamine; 5-HM), in the presence and absence of warfarin, were also detd. Relative to placebo, tolterodine had no discernible effect on the anti-coagulant actions of warfarin. Point ests. of the tolterodine-placebo ratios for prothrombin time and factor VII activity were 1.00 (90% confidence interval [CI]: 0.91-1.10) and 0.91 (90% CI: 0.83-0.99), resp. consistent with equivalence. No clin. significant changes in the pharmacokinetics of R-(+)- and S-(-)-warfarin were noted. Serum concn.-time profiles and the pharmacokinetics of tolterodine and 5-HM were similar in the presence and absence of warfarin. There were no safety concerns. These findings indicate that co-administration of tolterodine and warfarin is safe and well tolerated, with no clin. significant pharmacodynamic or kinetic interaction in healthy volunteers.

IT **207679-81-0**
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(coadministration of tolterodine and warfarin in relation to anticoagulant activity of warfarin and pharmacokinetics of both drugs)
RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:359788 CAPLUS
DOCUMENT NUMBER: 134:371775
TITLE: Pharmaceutical formulation containing tolterodine for bladder disorders
INVENTOR(S): Nilvebrant, Lisbeth; Hallen, Bengt; Olsson, Birgitta; Stroembom, Jan; Gren, Torkel; Ringberg, Anders; Wikberg, Martin
PATENT ASSIGNEE(S): Pharmacia AB, Swed.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034139	A1	20010517	WO 2000-SE2061	20001024
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2000027364	A1	20000518	WO 1999-SE2052	19991111
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000015346	A	20020625	BR 2000-15346	20001024
EP 1227806	A1	20020807	EP 2000-975092	20001024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003513918	T2	20030415	JP 2001-536139	20001024
NZ 518309	A	20030530	NZ 2000-518309	20001024
EE 200200245	A	20030616	EE 2002-245	20001024
NO 2002002264	A	20020513	NO 2002-2264	20020513

PRIORITY APPLN. INFO.: WO 1999-SE2052 A 19991111
SE 2000-782 A 20000309

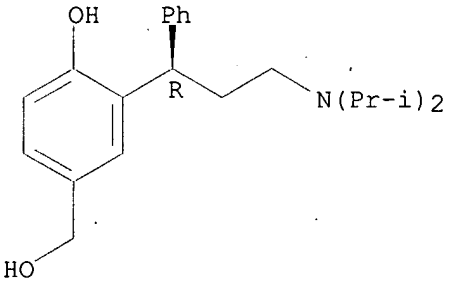
SE 1998-3871 A 19981111
WO 1999-SE1463 W 19990826
WO 2000-SE2061 W 20001024

AB The invention relates to a pharmaceutical formulation contg. tolterodine or a tolterodine-related compd., or a pharmacol. acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80 after 18 h, and after oral administration to a patient is capable of maintaining a substantially const. serum level of the active moiety or moieties for 24 h. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders. Controlled release beads and capsules comprising multilayers were prepd. contg. tolterodine L-tartrate were prepd.

IT **207679-81-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(pharmaceutical formulation contg. tolterodine for bladder disorders)

RN 207679-81-0 CAPLUS
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

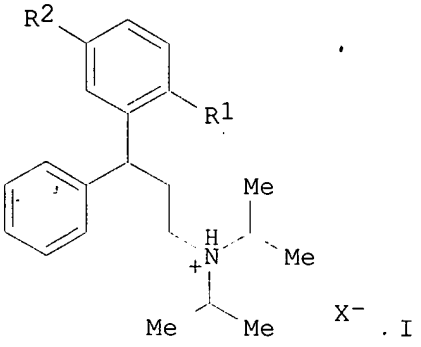


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:533448 CAPLUS
DOCUMENT NUMBER: 133:155419
TITLE: Stable salts of novel derivatives of 3,3-diphenylpropylamines
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Gebrauchsmusterschrift, 37 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 29923134	U1	20000803	DE 1999-29923134	19991116
DE 19955190	A1	20010621	DE 1999-19955190	19991116

PRIORITY APPLN. INFO.: DE 1999-19955190 IA 19991116
OTHER SOURCE(S): MARPAT 133:155419
GI

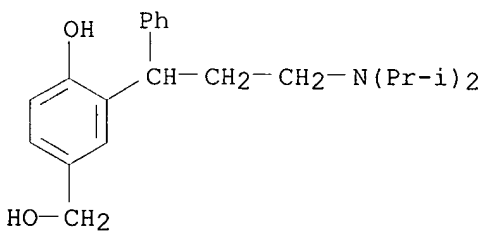


AB 3,3-Diphenylpropylamine salts I [R1 = RCO2; R = C1-6 alkyl, C3-10 cycloalkyl, (substituted) Ph; R2 = CH2OH; X = inorg. or org. acid] are prepd. for use as prodrugs of agents for treatment of urinary incontinence and other spasmogenic disorders. I show improved absorption through biol. membranes and improved metabolic patterns and are easily crystd. I are prepd. from I free base (R1 = PhCH2O, R2 = CO2Me) by debenzylation, redn., acylation, and combination with HX. Thus, R-(-)-I-HCl (R1 = PhCH2O, R2 = CO2H) was esterified by refluxing in acidic MeOH, the ester was reduced with LiAlH4, the resulting carbinol was reduced with Raney Ni/H2, and the product [R-(+)-I free base, R = CHMe2] was converted to its H fumarate salt by heating with equimolar fumaric acid in 2-butanone; the salt was crystd. by addn. of cyclohexanone and cooling to 0.degree..

IT **200801-70-3P 207679-81-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stable salts of novel derivs. of diphenylpropylamines)

RN 200801-70-3 CAPLUS

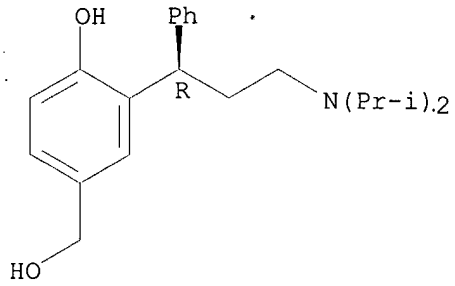
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)



RN 207679-81-0 CAPLUS

CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L121 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:167160 CAPLUS
DOCUMENT NUMBER: 131:13797
TITLE: Pharmacological effects of tolterodine on human isolated urinary bladder
AUTHOR(S): Yono, Makoto; Yoshida, Masaki; Wada, Yoshihiro; Kikukawa, Hiroaki; Takahashi, Wataru; Inadome, Akito; Seshita, Hiroshi; Ueda, Shoichi
CORPORATE SOURCE: Department of Urology, School of Medicine, Kumamoto University, Kumamoto, 860-8556, Japan
SOURCE: European Journal of Pharmacology (1999), 368(2/3), 223-230
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, is an antimuscarinic drug developed for the treatment of overactive bladder with symptoms of frequency, urgency and urge incontinence. The authors investigated the effects of tolterodine and its major active metabolite, DD 01 (PNU-200577), (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine, on the contractions induced by carbachol, KCl, CaCl2 and elec. field stimulation in human isolated urinary bladder smooth muscles, using the muscle bath technique. Specimens of human urinary bladder were obtained from 20 patients who underwent total cystectomy due to malignant bladder tumor. The detrusor prepns. were taken from the intact part of the dome region of the bladder. Carbachol (10-9-10-2 M) caused concn.-dependent contraction of human detrusor smooth muscles. Tolterodine (10-9-10-6 M), DD 01 (10-9-10-6 M), oxybutynin (10-8-10-6 M), propiverine (10-8-10-6 M), atropine (10-9-10-6 M), pirenzepine (10-8-10-5 M), methoctramine (10-8-10-5 M) and 4-diphenylacetoxy-N-methylpiperidine (4-DAMP) (10-9-10-6 M) caused typical shifts to the right of the concn.-response curves for carbachol, except for higher concns. (10-5 M) of oxybutynin and propiverine, which caused a decrease of about 30% of the max. contractile responses to carbachol. All the slopes of the regression lines of Schild plots were close to unity, and the rank order of pA2 values was: atropine = DD 01 = tolterodine = 4-DAMP = oxybutynin > propiverine = pirenzepine > methoctramine. Tolterodine (10-9-10-6 M) and DD 01 (10-9-10-6 M) did not inhibit the KCl-induced (80 mM) and CaCl2-induced (5 mM) contractions, while oxybutynin (10-8-10-5 M) and propiverine (10-8-10-5 M) significantly inhibited the contractions. Elec. field stimulation (2-60 Hz) caused frequency-dependent contraction of human detrusor smooth muscles, which were significantly inhibited by various drugs. In the presence of 10-6 M atropine, tolterodine and DD 01 did not inhibit the residual contractions induced by elec. field stimulation at any of the frequencies, while oxybutynin (10-5 M) and propiverine (10-5 M) significantly inhibited the atropine-resistant part of the contractions. The results suggest that the inhibitory effects of tolterodine and DD 01 are mediated only by their

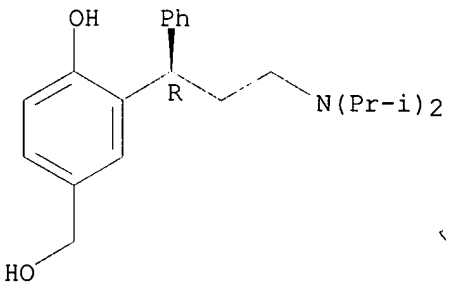
antimuscarinic action, which is equal to that of oxybutynin and significantly greater than that of propiverine, and that tolterodine and DD 01 have neither Ca2+ channel antagonist action nor inhibitory effect on the atropine-resistant part of the contractions in human detrusor smooth muscles. These findings support the usefulness of tolterodine as a therapeutic drug for overactive bladder with symptoms of frequency, urgency and urge incontinence.

IT **207679-81-0**, PNU-200577
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. effects of tolterodine and its metabolite on human isolated urinary bladder contraction)

RN 207679-81-0 CAPLUS

CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:682217 CAPLUS
DOCUMENT NUMBER: 129:316029
TITLE: Novel 3-aryl-3-phenylpropanamines with anticholinergic activity, their use in the treatment of urinary **incontinence**, and their preparation
INVENTOR(S): Johansson, Rolf; Haraldsson, Martin; Ringberg, Erik; Vagberg, Jan; Beierlein, Katarina; Emond, Rikard; Sjoberg, Birger
PATENT ASSIGNEE(S): Pharmacia and Upjohn AB, Swed.
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

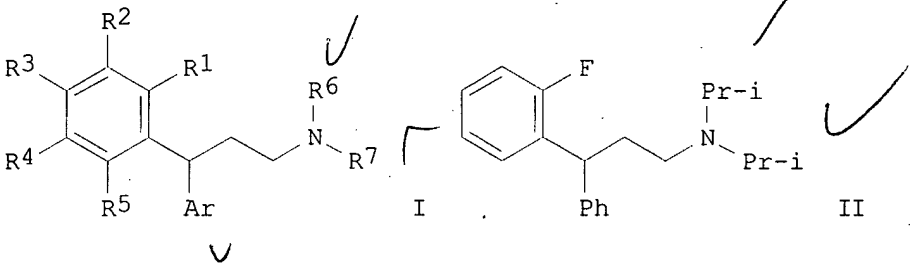
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843942	A1	19981008	WO 1998-SE556	19980326
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9802478	A	19981008	ZA 1998-2478	19980324
AU 9867552	A1	19981022	AU 1998-67552	19980326

AU 739186	B2	20011004			
BR 9808069	A	20000308	BR 1998-8069	19980326	
EP 1019358	A1	20000719	EP 1998-912864	19980326	
EP 1019358	B1	20030507			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2001522355	T2	20011113	JP 1998-541548	19980326	
AT 239693	E	20030515	AT 1998-912864	19980326	
NO 9904438	A	19991126	NO 1999-4438	19990913	
MX 9908862	A	20000228	MX 1999-8862	19990927	
US 6313132	B1	20011106	US 1999-381868	19990927	

PRIORITY APPLN. INFO.: SE 1997-1144 A 19970327
WO 1998-SE556 W 19980326

OTHER SOURCE(S): MARPAT 129:316029

GI



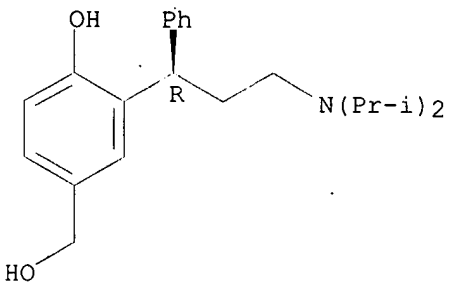
AB The invention relates to novel compds. I [wherein R1 = H, OH, alkyl, alkoxy, CF3, amino, alkanoylamino, alkanoyloxy, halo, hydroxyalkyl; R2, R3 = H, OH, alkyl, alkoxy, hydroxyalkyl, halo, carbamoyl, etc.; R4 = (un)substituted alkyl or amino, CHO, CO2H, NO2, cyano, N3, alkoxy, and may also be H, Me, OMe, etc. under some circumstances; R5 = H, halo, alkyl; Ar = (un)substituted (hetero)aryl; R6, R7 = hydrocarbyl with optional OH groups or O bridge(s), and may form a ring; with several provisos], their salts with physiol. acceptable acids, their racemic mixts., and the individual enantiomers. The compds. have anticholinergic activity, and in particular are of use in the treatment of urinary incontinence. Sixty synthetic examples are given, and approx. 90 compds. (including free bases and salts) were prepd. and/or claimed. For instance, Wittig-type reaction of (EtO)2P(O)CH2CON(Pr-iso)2 with 2-fluorobenzophenone, followed by hydrogenation of the formed olefin and redn. of the amide with LiAlH4, gave after acidification, title compd. II.HCl. In a test for inhibition of carbachol-induced contraction of isolated guinea pig bladder strips, II had a KB value of 10 nM, and other compds. had values ranging from 1.18 nM to 3315 nM.

IT **207679-81-0 214601-94-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; prepn. of arylphenylpropanamines as anticholinergic agents)

RN 207679-81-0 CAPLUS

CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

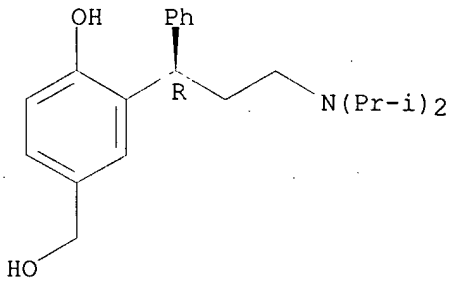


RN 214601-94-2 CAPLUS
CN Benzeneacetic acid, .alpha.-hydroxy-, compd. with 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

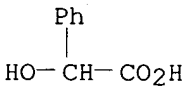
CRN 207679-81-0
CMF C22 H31 N O2

Absolute stereochemistry. Rotation (+).



CM 2

CRN 90-64-2
CMF C8 H8 O3



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L121 ANSWER 13 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:207991 USPATFULL
TITLE: Antimuscarinic aerosol
INVENTOR(S): Cammarata, Sue K., Portage, MI, UNITED STATES
Kolbasa, Karen, Schoolcraft, MI, UNITED STATES
Palandra, Joe, Kalamazoo, MI, UNITED STATES
Richards, Ivan, Kalamazoo, MI, UNITED STATES
Warchol, Mark P., Kalamazoo, MI, UNITED STATES

NUMBER	KIND	DATE

Searched by Barb O'Bryen, STIC 308-4291

PATENT INFORMATION: US 2003144352 A1 20030731
APPLICATION INFO.: US 2002-287061 A1 20021104 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-337298P	2001/11/05 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DINSMORE & SHOHL, LLP, 1900 CHEMED CENTER, 255 EAST FIFTH STREET, CINCINNATI, OH, 45202
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 681
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

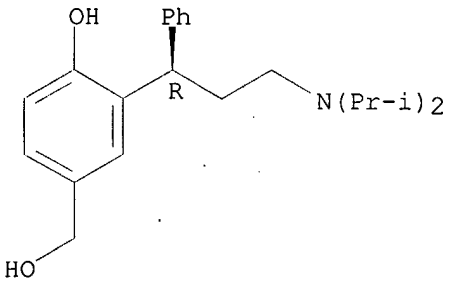
AB The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

The invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **207679-81-0**
(antimuscarinic inhalants for treatment of urinary disorder)
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L121 ANSWER 14 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:180352 USPATFULL
TITLE: Transdermally administered tolterodine as anti-muscarinic agent for the treatment of overactive bladder
INVENTOR(S): Jacobsen, Lene Orup, Gentofte, DENMARK
Kreilgard, Bo, Hillerod, DENMARK

Searched by Barb O'Bryen, STIC 308-4291

Hoeck, Ulla, Hillerod, DENMARK
Kristensen, Helle, Slangerup, DENMARK
PATENT ASSIGNEE(S): Pharmacia AB (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003124179	A1	20030703
APPLICATION INFO.:	US 2002-301719	A1	20021122 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-763654, filed on 30 Apr 2001, GRANTED, Pat. No. US 6517864 A 371 of International Ser. No. WO 1999-SE1464, filed on 26 Aug 1999, UNKNOWN

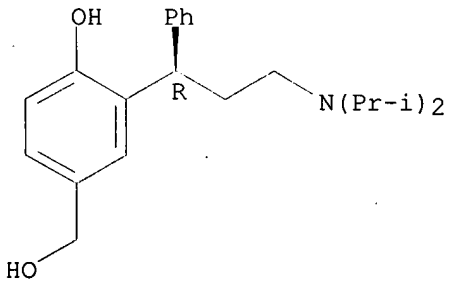
	NUMBER	DATE
PRIORITY INFORMATION:	SE 1998-2864	19980827

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 32 Drawing Page(s)
LINE COUNT: 1427
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is drawn to set of formulations of at least one compound selected from tolterodine, salts thereof, prodrugs thereof and/or metabolites thereof, wherein in the set of formulations contains at least one device for transdermal administration and at least one formulation for oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration, in order to achieve an effect against overactive **bladder** and/or symptoms associated with this condition. The present invention is further drawn to methods of treating an overactive **bladder** with the formulations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **207679-81-0**
(controlled-release tolterodine formulations)
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L121 ANSWER 15 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:38209 USPATFULL
TITLE: Tolterodine metabolites
INVENTOR(S): Aberg, A.K. Gunnar, Sarasota, FL, UNITED STATES

	NUMBER	KIND	DATE

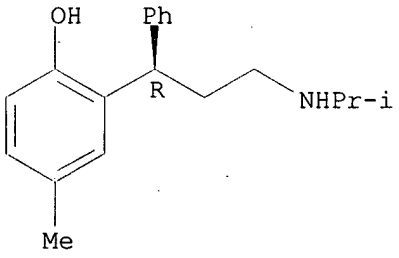
PATENT INFORMATION:	US 2003027856	A1	20030206
APPLICATION INFO.:	US 2001-895463	A1	20010629 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kevin S. Lemack, Nields & Lemack, Suite 8, 176 E. Main Street, Westboro, MA, 01581
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 462
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for treating **smooth muscle** hyperactivity, including urinary **incontinence**, while avoiding concomitant liability of adverse effects associated with tolterodine and the racemic version thereof are disclosed. The methods comprise administering a therapeutically effective amount of a mono-isopropyl metabolite or a parahydroxymethyl metabolite or a parahydroxymethyl mono-isopropyl metabolite of tolterodine or racemic versions thereof or a pharmaceutically acceptable salt of either metabolite. Pharmaceutical compositions in the form of tablets and transdermal devices comprising said compounds and acceptable carriers are also disclosed.

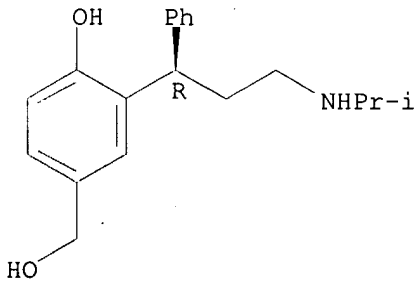
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **194482-41-2 194482-42-3 200801-70-3 207679-81-0 480432-14-2 480432-16-4**
(tolterodine metabolites for treatment of **smooth muscle** hyperactivity)
RN 194482-41-2 USPATFULL
CN Phenol, 4-methyl-2-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



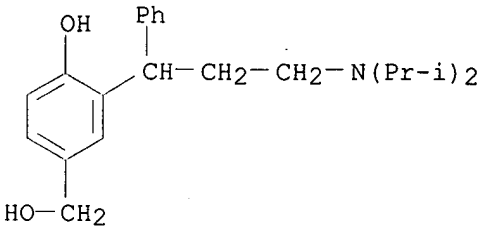
RN 194482-42-3 USPATFULL
CN Benzenemethanol, 4-hydroxy-3-[(1R)-3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



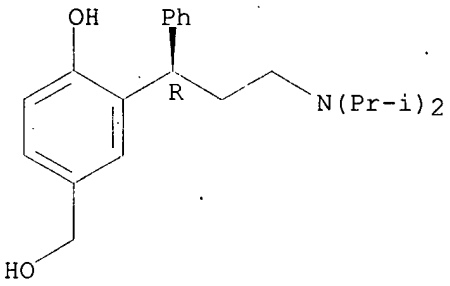
RN 200801-70-3 USPATFULL

CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

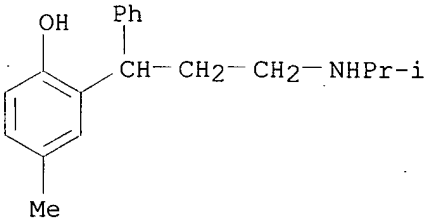


RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

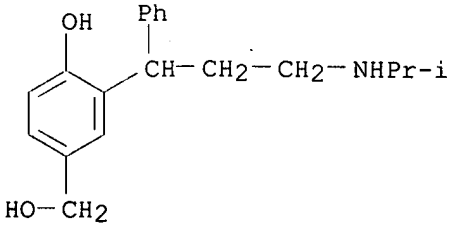
Absolute stereochemistry. Rotation (+).



RN 480432-14-2 USPATFULL
CN Phenol, 4-methyl-2-[3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



RN 480432-16-4 USPATFULL
CN Benzenemethanol, 4-hydroxy-3-[3-[(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



L121 ANSWER 16 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:40432 USPATFULL
TITLE: Transdermally administered tolterodine as anti-muscarinic agent for the treatment of overactive **bladder**
INVENTOR(S): Orup Jacobsen, Lene, Gentofte, DENMARK
Kreilgard, Bo, Hillerod, DENMARK
Hoeck, Ulla, Hillerod, DENMARK
Kristensen, Helle, Slangerup, DENMARK
PATENT ASSIGNEE(S): Pharmacia AB, Stockholm, SWEDEN (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6517864	B1	20030211	
	WO 2000012070		20000309	
APPLICATION INFO.:	US 2001-763654		20010430	(9)
	WO 1999-SE1464		19990826	

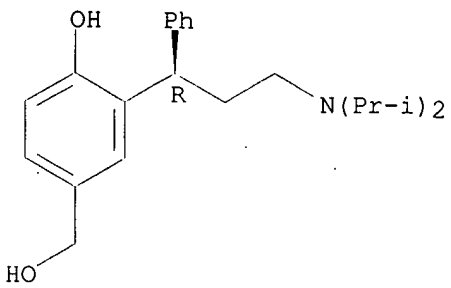
	NUMBER	DATE
PRIORITY INFORMATION:	SE 1998-2864	19980827

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Sheikh, Humera N.
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 35 Drawing Figure(s); 32 Drawing Page(s)
LINE COUNT: 1381
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Device for transdermal administration of tolterodine, optionally encompassing salts, prodrugs and metabolites thereof, optionally together with pharmaceutically acceptable carrier(s) to a human being or an animal in order to achieve an effect against overactive **bladder**. Use of a compound having an effect against overactive **bladder** comprising tolterodine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), for the manufacture of a composition to be administered transdermally for achieving an effect against overactive **bladder**. Method for achieving an effect against overactive **bladder** in a living body by transdermal administration of a compound comprising tolterodine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **207679-81-0**
(controlled-release tolterodine formulations)
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



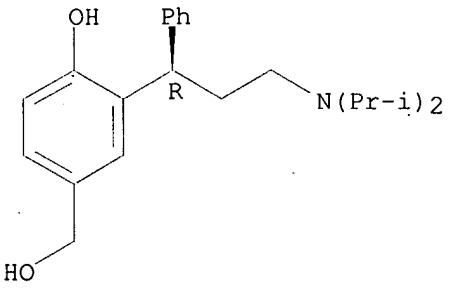
L121 ANSWER 17 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2001:197029 USPATFULL
TITLE: Therapeutically active diarylpropylamines; their pharmaceutically acceptable salts; a method for their preparation and method for their use
INVENTOR(S): Johansson, Rolf, Huddinge, Sweden
Haraldsson, Martin, Taby, Sweden
Ringberg, Erik, Uppsala, Sweden
Vagberg, Ian, Sollentuna, Sweden
Beierlein, Katarina, Uppsala, Sweden
Emond, Rikard, Saltsjobaden, Sweden
Sjoberg, Birger, Sollentuna, Sweden
PATENT ASSIGNEE(S): Pharmacia AB, Stockholm, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6313132	B1	20011106	
	WO 9843942		19981008	
APPLICATION INFO.:	US 1999-381868		19990927	(9)
	WO 1998-SE556		19980326	
			19990927	PCT 371 date
			19990927	PCT 102(e) date

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Oswecki, Jane C.
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 2364
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to novel compounds of Formula (I) wherein R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5, R.sup.6, R.sup.7 and Ar are as defined in claim 1, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. The compounds have anticholinergic activity, and the invention also relates to the compounds of Formula (I), the use of the compounds of Formula (I) for preparing anticholinergic drugs, the use of the compounds of Formula (I) for treating urinary tract **incontinence**, and methods for preparing the compounds of Formula (I). ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **207679-81-0 214601-94-2**
(starting material; prepn. of arylphenylpropanamines as anticholinergic agents)
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

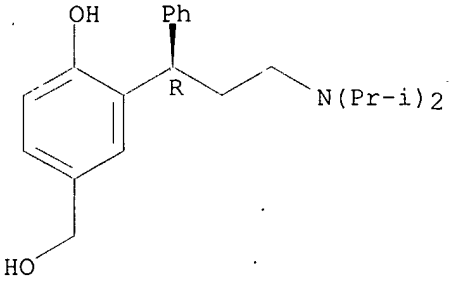


RN 214601-94-2 USPATFULL
CN Benzeneacetic acid, .alpha.-hydroxy-, compd. with 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

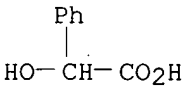
CRN 207679-81-0
CMF C22 H31 N O2

Absolute stereochemistry. Rotation (+).



CM 2

CRN 90-64-2
CMF C8 H8 O3



L121 ANSWER 18 OF 21 USPATFULL on STN
ACCESSION NUMBER: 97:104490 USPATFULL
TITLE: 3,3-diphenylpropylamines, their use and preparation
INVENTOR(S): Johansson, Rolf Arne, Huddinge, Sweden
Moses, Pinchas, Satsjo-Boo, Sweden
Nilvebrant, Lisbeth, Bromma, Sweden
Sparf, Bengt .ANG.ke, Tr.ang.ngsund, Sweden
PATENT ASSIGNEE(S): Pharmacia AB, Stockholm, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5686464		19971111

APPLICATION INFO.: US 1996-684638 19960722 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1995-432113, filed on 5 May 1995, now patented, Pat. No. US 5559269

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-3318	19921106

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Krass, Frederick
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 628
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

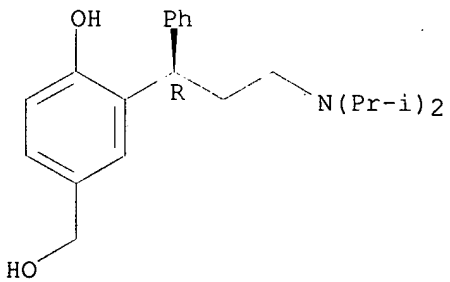
AB A 3,3-diphenylpropylamine of the formula I, or its physiologically acceptable acid salt thereof: ##STR1## wherein R.sup.1 represents hydrogen or methyl, R.sup.2 and R.sup.3 independently represent hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II ##STR2## wherein R.sup.4 and R.sup.5 independently represent a hydroxy substituted or unsubstituted non-aromatic hydrocarbyl group which can join together to form a ring and which together contain at least three carbon atoms, wherein at least one of R.sup.4 and R.sup.5 is hydroxy substituted, is useful in treating acetylcholine-mediated disorders such as urinary **incontinence**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **156755-20-3P 156755-22-5P 207679-81-0P 260389-90-0P**
(prepn. of, as anticholinergic)
RN 156755-20-3 USPATFULL
CN Benzeneacetic acid, .alpha.-hydroxy-, (.alpha.S)-, compd. with 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 207679-81-0
CMF C22 H31 N O2

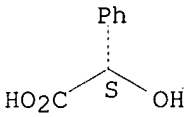
Absolute stereochemistry. Rotation (+).



CM 2

CRN 17199-29-0
CMF C8 H8 O3

Absolute stereochemistry. Rotation (+).

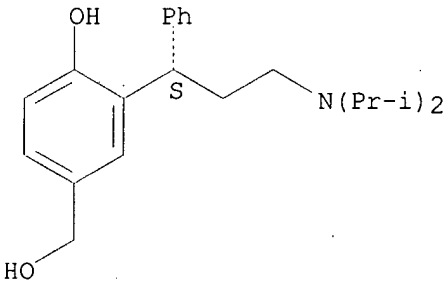


RN 156755-22-5 USPATFULL
CN Benzeneacetic acid, .alpha.-hydroxy-, (.alpha.S)-, compd. with 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 260389-90-0
CMF C22 H31 N O2

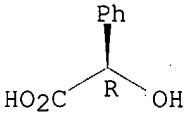
Absolute stereochemistry. Rotation (-).



CM 2

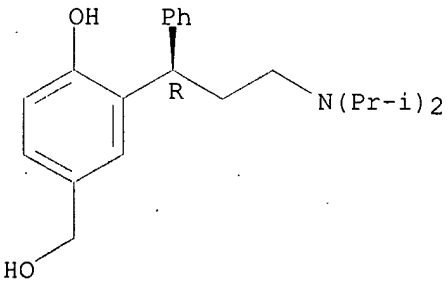
CRN 611-71-2
CMF C8 H8 O3

Absolute stereochemistry. Rotation (-).



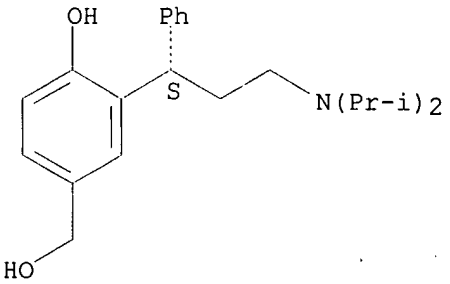
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 260389-90-0 USPATFULL
CN Benzenemethanol, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L121 ANSWER 19 OF 21 USPATFULL on STN
ACCESSION NUMBER: 96:87757 USPATFULL
TITLE: 3,3-diphenylpropylamines, their use and preparation
INVENTOR(S): Johansson, Rolf A., Huddinge, Sweden
Moses, Pinchas, Satsj o-Boo, Sweden
Nilvebrant, Lisbeth, Bromma, Sweden
Sparf, Bengt .ANG.., Tr.ang.ngsund, Sweden
PATENT ASSIGNEE(S): Pharmacia AB, Stockholm, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5559269		19960924	
APPLICATION INFO.:	US 1995-432113		19950505	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1992-3318	19921106

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hamilton, III, Thomas
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 674
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to 3,3-diphenylpropylamines of formula (I), wherein R.sup.1 signifies hydrogen or methyl, R.sup.2 and R.sup.3 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula (II), wherein R.sup.4 and R.sup.5 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R.sup.4 and R.sup.5 may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers. The invention also relates to methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs ##STR1##

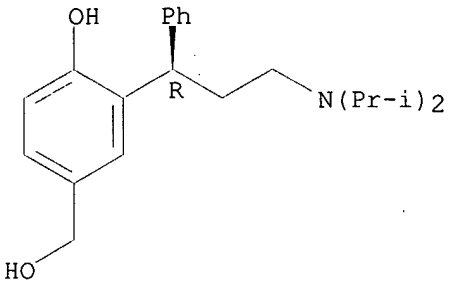
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **156755-20-3P 156755-22-5P 207679-81-0P**
260389-90-0P
(prepn. of, as anticholinergic)

RN 156755-20-3 USPATFULL
CN Benzeneacetic acid, .alpha.-hydroxy-, (.alpha.S)-, compd. with 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 207679-81-0
CMF C22 H31 N O2

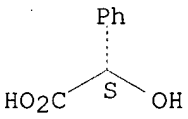
Absolute stereochemistry. Rotation (+).



CM 2

CRN 17199-29-0
CMF C8 H8 O3

Absolute stereochemistry. Rotation (+).

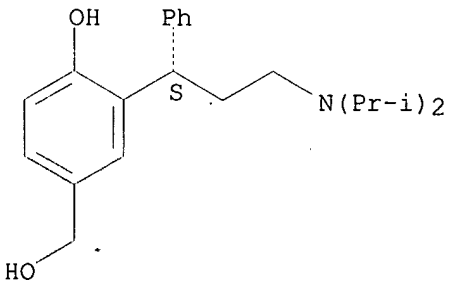


RN 156755-22-5 USPATFULL
CN Benzeneacetic acid, .alpha.-hydroxy-, (.alpha.S)-, compd. with 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxybenzenemethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 260389-90-0
CMF C22 H31 N O2

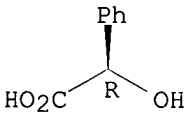
Absolute stereochemistry. Rotation (-).



CM 2

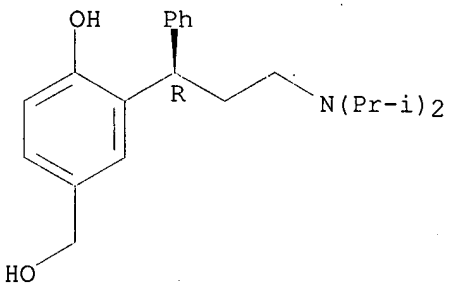
CRN 611-71-2
CMF C8 H8 O3

Absolute stereochemistry. Rotation (-).



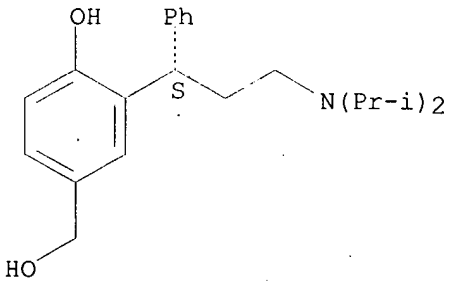
RN 207679-81-0 USPATFULL
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 260389-90-0 USPATFULL
CN Benzenemethanol, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L121 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:376634 BIOSIS
DOCUMENT NUMBER: PREV200200376634
TITLE: Effect of muscarinic antagonists on micturition pressure measured by cystometry in normal, conscious rats.
AUTHOR(S): Modiri, Ali-Reza (1); Alberts, Peteris; Gillberg, Per-Goran
CORPORATE SOURCE: (1) Department of Pharmacology, Biovitrum, UF5-1, Box 6443, Uppsala, SE-751 37 Sweden
SOURCE: Urology, (June, 2002) Vol. 59, No. 6, pp. 963-968. http://www.elsevier.com/locate/urologyonline. print.

Searched by Barb O'Bryen, STIC 308-4291

ISSN: 0090-4295.
DOCUMENT TYPE: Article
LANGUAGE: English
ABSTRACT:
Objectives: To establish an in vivo model to screen new muscarinic antagonists for the treatment of overactive urinary bladder and to calculate the respective ID50 values. Methods: The conscious rat cystometry model was modified to determine a complete dose-response curve in each animal. Spontaneous micturition was induced by infusion of room-temperature saline into rat bladders at a constant rate of 12 mL/hr. Cumulative doses of muscarinic antagonists administered in the femoral vein caused dose-dependent inhibition of the urinary bladder contraction measured as the micturition pressure. In addition, the in vitro pKB values for atropine, PNU-200577 (DD01), tolterodine, oxybutynin, and terodiline were determined in carbachol-contracted rat bladder strips. Results: The rank order of the in vivo ID50 values were atropine (14+-4 nmol/kg), PNU-200577 (22+-12 nmol/kg), tolterodine (94+-20 nmol/kg), oxybutynin (175+-89 nmol/kg), darifenacin (236+-144 nmol/kg), desethyloxybutynin (313+-209 nmol/kg), propiverine (4561+-2079 nmol/kg), and terodiline (18,339+-5348 nmol/kg). Tolterodine and PNU-200577 caused a parallel shift of the in vitro concentration-response curve to the right and did not alter the maximal contraction. The ID50 values correlated significantly with the in vitro rat pKB and human bladder pA2 values. Conclusions: The present results suggest that the rat cystometry model can be used in in vivo screening for new muscarinic antagonists.
CONCEPT CODE: Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
Urinary System and External Secretions - Physiology and Biochemistry *15504
Urinary System and External Secretions - Pathology *15506
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Cardiovascular System *22010
Pharmacology - Neuropharmacology *22024
BIOSYSTEMATIC CODE: Muridae 86375
INDEX TERMS: Major Concepts
Pharmacology; Urinary System (Chemical Coordination and Homeostasis)
INDEX TERMS: Parts, Structures, & Systems of Organisms
urinary bladder: excretory system
INDEX TERMS: Diseases
urinary bladder overactivity: drug therapy, urologic disease
INDEX TERMS: Chemicals & Biochemicals
PNU-200577 [DD01]: intravenous administration, muscarinic antagonist, pharmacokinetics; carbachol: autonomic - drug, cholinergic - drug; oxybutynin: intravenous administration, muscarinic antagonist, pharmacokinetics; terodiline: calcium channel blocker - drug, intravenous administration, muscarinic antagonist, pharmacokinetics; tolterodine: intravenous administration, muscarinic antagonist, pharmacokinetics
INDEX TERMS: Methods & Equipment
cystometry: evaluation method
INDEX TERMS: Miscellaneous Descriptors
drug dosage; micturition pressure
ORGANISM: Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISM: Organism Name
Sprague-Dawley rat (Muridae): animal model
ORGANISM: Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

REGISTRY NUMBER: **207679-81-0** (PNU-200577) structure printed at end of search
51-83-2 (CARBACHOL)
5633-20-5 (OXYBUTYNIN)
15793-40-5 (TERODILINE)
124937-51-5 (TOLTERODINE)

L121 ANSWER 21 OF 21 TOXCENTER COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:178220 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA135172358522
TITLE: Multiple dose pharmacokinetics of a new once daily extended release tolterodine formulation versus immediate release tolterodine
AUTHOR(S): Olsson, Birgitta; Szamost, Johan
CORPORATE SOURCE: Experimental Medicine, Biovitrum, Division of Pharmacia, Stockholm, Swed..
SOURCE: Clinical Pharmacokinetics, (2001) Vol. 40, No. 3, pp. 227-235.
CODEN: CPKNDH. ISSN: 0312-5963.
COUNTRY: SWEDEN
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2001:341549
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020319

ABSTRACT:
Objective: To det. the multiple dose pharmacokinetics of a new extended release (ER) capsule formulation of tolterodine, compared with the existing immediate release (IR) tablet, in healthy volunteers. Design: Nonblind, randomized, 2-way crossover trial. Participants: 19 healthy volunteers (7 females, 12 males), mean age 33 yr (range 18 to 55 yr). Prior to the study, all volunteers were classified as either extensive or poor metabolizers by cytochrome P 450 2D6 genotyping. Methods: Volunteers received tolterodine ER 4mg once daily or tolterodine IR 2mg twice daily for 6 days (all doses given as the L-tartrate salt). A washout period of 7 days sepd. the 2 treatments. Serum concns. of tolterodine, its active 5-hydroxymethyl metabolite (5-HM) and the active moiety (extensive metabolizers: sum of unbound tolterodine + 5-HM; poor metabolizers: unbound tolterodine) were measured for up to 48 h post-dose on day 6 (steady state). Tolerability was also detd. Results: 17 volunteers (13 extensive metabolizers, 4 poor metabolizers) completed the study and were evaluable for both treatment periods. The 90% confidence interval for the geometric mean ratio of area under the serum concn.-time curve to 24 h (AUC24) of the active moiety, for all volunteers combined, indicated equivalence for the 2 formulations. Pooled anal. also demonstrated that the peak serum concn. (Cmax) of the active moiety following administration of tolterodine ER was around 75% of that obsd. for the IR tablet, whereas the trough concn. was around 1.5-fold higher. Overall, the pharmacokinetics of tolterodine (irresp. of genotype) and 5-HM (extensive metabolizers only) were consistent with sustained drug release over 24 h. Tolterodine ER was well tolerated. Conclusions: The new once daily ER formulation of tolterodine 4mg shows pharmacokinetic equivalence (AUC24) to the existing IR tablet given at a dose of 2mg twice daily. Findings of lower Cmax for tolterodine ER may explain the significantly lower rate of dry mouth subsequently obsd. in patients with overactive bladder.

CLASSIFICATION CODE: 1-2
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
tolterodine pharmacokinetics delivery system genotype CYP2D6
REGISTRY NUMBER: 124937-51-5 (Tolterodine)
REGISTRY NUMBER: **200801-70-3** printed at end

=> fil reg; s 200801-70-3 or 207679-81-0

FILE 'REGISTRY' ENTERED AT 14:31:18 ON 15 SEP 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2003 HIGHEST RN 585509-69-9
DICTIONARY FILE UPDATES: 14 SEP 2003 HIGHEST RN 585509-69-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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             1 200801-70-3
               (200801-70-3/RN)
             1 207679-81-0
               (207679-81-0/RN)
L122         2 200801-70-3 OR  207679-81-0
```
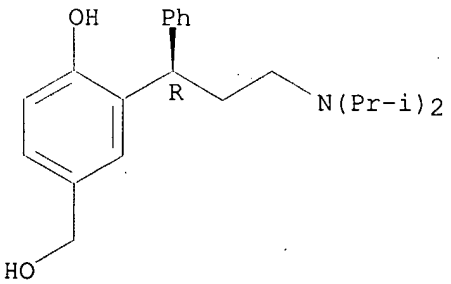

=> d ide 1-2; fil hom

L122 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN **207679-81-0** REGISTRY
CN Benzenemethanol, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5-Hydroxymethyltolterodine
CN PNU 200577
FS STEREOSEARCH
DR 156755-19-0
MF C22 H31 N O2
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USPAT2, USPATFULL

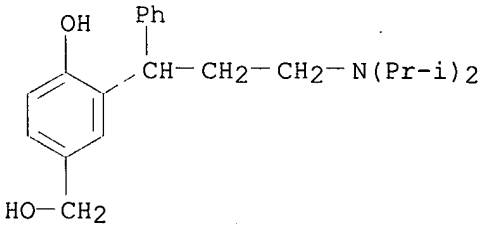
Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

30 REFERENCES IN FILE CA (1937 TO DATE)
30 REFERENCES IN FILE CAPLUS (1937 TO DATE)

L122 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS on STN
RN **200801-70-3** REGISTRY
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H31 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1937 TO DATE)
8 REFERENCES IN FILE CAPLUS (1937 TO DATE)

FILE 'HOME' ENTERED AT 14:31:24 ON 15 SEP 2003